Remarks

Claims 1-3, 8, 15, and 18-32 were pending in the subject application. By this Amendment, claims 18, 19, 21, 25, 26, and 30 have been amended, claims 1-3, 8, 15, 20, 27-29, and 32 have been cancelled, and new claims 33-43 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicants' agreement with or acquiescence in the Examiner's position. Accordingly, claims 18, 19, 21-26, 30, 31, and 33-43 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The applicants note that new claims 40-43 are drawn to a non-elected invention. The applicants reserve the right to request rejoinder of claims 40-43 upon an indication of an allowable product claim in accordance with MPEP §821.04.

Support in the specification for the amendments to claim 18 can be found, for example, at page 8, lines 26-29, page 9, lines 1-6, page 15, lines 11-29, and page 16, lines 1-7 ("process-forming", "neuronal cells"); page 15, lines 15-17 ("of the central nervous system"); page 3, lines 1-4, page 7, lines 6-12, page 19, lines 11-17, and Figures 4A-4C ("lacking processes", "no attachment"); page 7, lines 21-28, page 9, lines 7-20 ("culture medium"); page 3, lines 1-13, page 4, lines 3-20, page 17, lines 24-27 ("solid substrate supporting said culture medium"); page 7, lines 6-12, page 17, lines 24-27, Example 1, and Figures 4A-4C ("clustered into one or more aggregates suspended in said culture medium"); and page 7, lines 13-20 ("calcium concentration of 100 μM or less"). Support for the amendment to claim 21 can be found, for example, at page 4, lines 11-12 and 18-20, page 5, lines 1-8, and page 17, lines 24-27, of the specification. Support for the amendment to claim 25 can be found, for example, at page 4, lines 18-20, and page 5, lines 1-8 and 23-25, of the specification. Claim 26 has been amended to correct an obvious typographical error. Support for the amendment to claim 26 can be found at page 7, lines 15-16, of the specification. Claim 30 has been reworded to be consistent with claim 18 as currently amended. Support for new claim 33 can be found, for example, at page 7, lines 16-20, of the specification. Support for new claim 34 can be

found, for example, at page 8, lines 9-11, of the specification. Support for new claims 35 and 36 can be found, for example, at page 8, lines 9-14, of the specification. Support for new claim 37 can be found, for example, at page 15, lines 20-29, and page 16, lines 1-7, of the specification. Support for claim 38 can be found, for example, at page 9, lines 27-29, of the specification. Support for new claim 39 can be found, for example, at page 4, lines 8-12, page 7, lines 6-20, page 8, line 26, page 9, lines 8-10, page 15, lines 15-17, and Example 1 at pages 18-19 (*e.g.*, page 19, lines 11-16), of the specification. Support for new claims 40 and 41 can be found, for example, at page 2, lines 1-28, page 7, lines 6-12, Example 1 at pages 18-19, of the specification, and the claims as originally filed. Support for new claims 42 and 43 can be found, for example, at page 8, lines 15-18, and page 10, lines 4-20, of the specification.

Claims 18-31 have been rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. The Office Action indicates that the subject specification does not provide a sufficient written description of cell attachment factors or cell attachment treatments, as recited in claim 18.

The applicants submit that the specification adequately describes the claimed subject matter. However, by this Amendment, the applicants have amended claim 18 to recite that the cell culture comprises process-forming neuronal cells of the central nervous system (CNS), culture medium, and a solid substrate, wherein the neuronal cells lack processes and are clustered into one or more aggregates suspended in the culture medium, and wherein there is no attachment of the neuronal cells to the substrate. The rejected claims no longer recite "cell attachment factors" or "cell attachment treatments". In addition, new claim 39 does not recite "cell attachment factors" or "cell attachment treatments".

Thus, the applicants submit that the subject specification contains sufficient disclosure to convey to one of ordinary skill in the art that the applicants had possession of the concept of what is claimed, which is all that is necessary to satisfy the written description requirement of 35 U.S.C. §112, first paragraph. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 20, 25, and 29 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The Office Action indicates that the specification does not

enable any type of process-forming cells, wherein there is substantially no attachment of the process-forming cells.

The applicants respectfully traverse and submit that the claims are fully enabled by the subject specification. However, as indicated above, the applicants have amended independent claim 18, from which claims 20 and 25 depend, to recite that the cell culture comprises process-forming neuronal cells of the CNS; culture medium; and a solid substrate, wherein the neuronal cells lack processes and are clustered into one or more aggregates suspended in the culture medium, and wherein there is no attachment of the neuronal cells to the substrate. At page 4, first full paragraph, the Office Action acknowledges that the specification is "enabling for a cell culture comprising one or more process-forming neuronal cells, wherein there is substantially no attachment of the neuronal cells to the substrate." Claim 29 has been cancelled. New claim 39 also recites that the cell culture comprises process-forming neuronal cells of the CNS and that there is no attachment of the neuronal cells to the plate.

As the Examiner is aware, a specification is initially presumed to be in compliance with the enablement requirement of §112, first paragraph. The burden is on the Patent Office to establish a reasonable basis to question enablement. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The test of enablement is whether one of ordinary skill in the art could make and use the claimed invention from the teachings of the patent application, coupled with information known in the art, without undue experimentation. For an Office Action to sustain a rejection on the grounds of enablement, it must provide evidence that the claimed method could not be performed without undue experimentation.

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. *In re Fisher*, 427 F.2d 833, 839; 166 USPQ 18, 24 (CCPA 1970). The specification need not even contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908; 164 USPQ 642, 645 (CCPA 1970) and MPEP 2164.02.

Thus, the applicants respectfully submit that the scope of the claims is commensurate with the scope of the enabling disclosure, and one of ordinary skill in the art could make and use the subject invention without the need for undue experimentation. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 18-31 have been rejected under 35 U.S.C. §112, second paragraph, as indefinite. The applicants respectfully submit that one of ordinary skill in the art is able to ascertain with a reasonable degree of precision and particularity, the area set out and circumscribed by the claims. However, as indicated above, the claims as currently amended no longer recite "cell attachment treatments" or "cell attachment factors". Claim 20 has been cancelled and claim 25 has been amended to remove the term "substantially". Claim 18 has been amended to provide antecedent basis for the phrase "said solid substrate" in claim 25. The applicants respectfully submit that one of ordinary skill in the art would appreciate that a solid substrate, such as a culture dish, supports cells placed on or within the substrate, whether the cells are in direct contact with the substrate or not. As stated at page 17, lines 24-27, of the subject specification, "where the cells are described as being 'supported by' a solid substrate, it is intended to include the situation where the substrate is supporting culture media containing the cells, wherein the cells are suspended in the culture media and not attached to the substrate". Under such circumstances, the solid substrate supports the culture media, which supports the cells; hence, the substrate indirectly supports the cells. Nonetheless, claim 18 has been amended to recite that the solid substrate supports the culture medium in which the neuronal cell aggregates are suspended. Claim 26 has been amended replace the term "50 μm" with "50 μM" (50 micromolar). Claim 29 has been cancelled. In view of the foregoing remarks and amendments to the claims, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claims 18, 21-22, 24, and 29-31 have been rejected under 35 U.S.C. §102(b) as being anticipated by Steinman *et al.* (U.S. Patent No. 5,994,126). The applicants respectfully submit that the Steinman *et al.* patent does not teach or suggest the cell culture of the subject invention. As indicated above, by this Amendment, the applicants have amended claim 18 to recite that the cells of the culture are process-forming neuronal cells of the CNS. New claim 39 also recites that the

process-forming cells are neuronal cells of the CNS. In contrast, the Steinman *et al.* patent relates to methods for expanding and differentiating dendritic cell precursors from human blood, resulting in cultures of mature dendritic cells. As taught at columns 1-4 of the Steinman *et al.* patent, dendritic cells are specialized, phagocytic, antigen-presenting cells of the immune system. Although dendritic cells have processes (dendrites) during certain stages of their development, as do neurons, they are unrelated to neuronal cells.

As the Examiner is aware, to be anticipatory under 35 U.S.C. §102(b), a reference must disclose within the four corners of the document each and every element and limitation contained in the rejected claim. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ 2d 1001, 1010 (Fed. Cir. 1991). The applicants respectfully submit that the Steinman *et al.* patent does not teach or suggest every element of the applicants' claimed invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Claims 18, 21-25, and 30 are rejected under 35 U.S.C. §102(b) as being anticipated by Weiss *et al.* (U.S. Patent 5,981,165). The applicants respectfully submit that the Weiss *et al.* patent does not teach or suggest the cell culture of the subject invention. However, by this Amendment, the applicants have amended claim 18 to recite that the culture has a calcium concentration of 100 μM or less, as recited in claim 20 (now cancelled). New claim 39 also recites that the culture has a calcium concentration of 100 μM or less. The Weiss *et al.* patent does not teach or suggest a cell culture having the recited calcium concentration. As indicated above, a reference must disclose each and every element and limitation contained in the rejected claim in order to be anticipatory. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Claims 18, 19, 21, 25, and 27-29 have been rejected under 35 U.S.C. §102(b) as being anticipated by Takazawa *et al.* (U.S. Patent No. 5,219,752). The applicants respectfully submit that the Takazawa *et al.* patent does not teach or suggest the cell culture of the subject invention.

The Takazawa *et al.* patent proposes that various adherent animal cells can be cultured using the method disclosed therein. Furthermore, among the myriad of cell lines (over 500) listed in the table spanning columns 5-12, representing cells from a diverse variety of tissues, which the Takazawa *et al.* patent proposes can be cultured using the disclosed method, two mouse neuroblastoma cell lines, NB41A3 (ATCC No. CCL 147) and Neuro-2a (ATCC No. CCL 131), are

listed (column 11, lines 12-13). However, the only cells described as actually being cultured with the disclosed method are kidney cells, *i.e.*, 293 cells (human fetal kidney) and BHK 229 cells (hamster kidney).

The applicants have amended claim 18 to recite that the cells of the culture are process-forming neuronal cells of the CNS. New claim 39 also recites that the cells of the culture are process-forming neuronal cells of the CNS. The Takazawa *et al.* patent does not teach or suggest a cell culture comprising process-forming neuronal cells of the CNS. The applicants note that the mouse neuroblastoma cell lines, NB41A3 and Neuro-2a, are cells of the peripheral nervous system (PNS). The cited reference does not disclose each and every element and limitation contained in the rejected claims. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Claims 18, 21-24, and 27 have been rejected under 35 U.S.C. §102(e) as being anticipated by Grinstaff *et al.* (U.S. Published Application No. 2003/0185870). The applicants respectfully submit that the Grinstaff *et al.* publication does not teach or suggest the cell culture of the subject invention. The Grinstaff *et al.* publication describes a cell culture method that utilizes an interfacial biomaterial comprising a plurality of binding agents, wherein the biomaterial is situated as a layer or coating interposed between the cells and the non-biological substrate, binding both (see paragraph [0029] at page 3). Paragraphs [0318] and [0319] of the Grinstaff *et al.* publication indicate that when the interfacial biomaterial was coated on a polystyrene culture plate and human fibroblasts and endothelial cells were subsequently seeded, the cells were "not tightly adhered to the surface." As indicated above, claim 18 now recites that the cells of the culture are process-forming neuronal cells of the CNS, which are clustered into one or more aggregates suspended in the culture medium. New claim 39 also recites that the cells are process-forming neuronal cells of the CNS, which are clustered into one or more aggregates. The Grinstaff *et al.* publication does not describe a cell culture of neuronal cells of the CNS lacking processes, or their assembly into aggregates, suspended or otherwise. As indicated above, a reference must disclose each and every element and limitation contained in the rejected claim in order to be anticipatory. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(e) is respectfully requested.

Claims 18-26 and 28-29 have been rejected under 35 U.S.C. §102(a) as being anticipated by Andrews *et al.* (Poster presentation from Cell Culture and Engineering Conference in Snowmass, CO, 2002). The applicants respectfully traverse these grounds for rejection and submit that the Andrews *et al.* presentation does not teach or suggest the invention as currently amended, and is not prior art to the claimed invention. As indicated above, the applicants have amended claim 18 to recite that the culture has a calcium concentration of 100 μM or less. As acknowledged by the Examiner, the Andrews *et al.* presentation is silent regarding calcium concentration. The applicants respectfully submit that the presence of inherent matter must be grounded on more than speculation, it must be a certainty. *Ethyl Molded Product Co. v. Betts Package Inc.*, 9 USPQ 2d 1001, 1032-1033 (I.D.KY 1988) ("the doctrine of inherency is available only when the prior inherent event can be established as a certainty. That an event may result from a given set of circumstances is not sufficient to establish anticipation" (emphasis added)). Furthermore, when the reference is silent about the asserted inherent characteristic, while such a gap in the reference may be filled with recourse to extrinsic evidence, the extrinsic evidence

> must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 49 USPQ 2d 1949, 1950-1951 (Fed. Cir. 1999).

There is no teaching in the Andrews *et al.* presentation regarding calcium concentration, nor has the Examiner shown that it is a certainty that the cell culture described in the Andrews *et al.* presentation has the recited calcium concentration. To be prior art under section 102, a reference must be enabling, placing the claimed invention in the hand of one skilled in the art.

> Simply stated, a prior publication or patent description will be considered as anticipatory when its disclosure is at once specific and enabling with regard to the particular subject matter at issue ... However, such disclosure may yet be held not to legally anticipate the claimed subject matter if it is found not be sufficiently enabling, in other words, if it does not place the subject mater of the claims within "the possession of the public" (emphasis added). *In re Wilder*, 166 USPQ 545, 548 (CCPA 1970).

Moreover, the Andrews *et al.* presentation is not prior art to the claimed invention. As the Examiner is undoubtedly aware, the requirements for authorship and inventorship are not the same. The inventorship of the claimed invention and the authorship of the Andrews *et al.* presentation differ in that although Thomas B. Freeman, Christian Arriagada, and Julio Salazar Rivera are inventors on the subject application, they are not co-authors of the Andrews *et al.* presentation. Furthermore, the inventorship of the claimed invention and the authorship of the Andrews *et al.* publication differ in that although P. Venegas (Paola Venegas) is a co-author of the Andrews *et al.* presentation, she is not named as an inventor on the subject application. Thus, P. Caviedes (Pablo Caviedes), R. Caviedes (Raul Caviedes), J.A. Asenjo (Juan A. Asenjo), B.A. Andrews (Barbara A. Andrews), and D. Sepulveda (Dario Sepulveda), are co-authors of the Andrews *et al.* presentation and are inventors on the subject application.

Submitted herewith for the Examiner's consideration is a Declaration under 37 C.F.R. §1.132 by Dr. Pablo Caviedes, an inventor of the subject application. Dr. Caviedes explains in his Declaration that although P. Venegas was acknowledged as a co-author of the Andrews *et al.* presentation, she did not contribute to the conception of the claimed invention. Therefore, despite her helpful assistance in the laboratory, she was not included as a co-inventor on the subject application. Furthermore, as indicated by Dr. Caviedes in his Declaration, Thomas B. Freeman, Christian Arriagada, and Julio Salazar Rivera contributed to the claimed invention, but the experimental data produced during their research was not included in the Andrews *et al.* presentation. Therefore, Thomas B. Freeman, Christian Arriagada, and Julio Salazar Rivera were not included as co-authors of the Andrews *et al.* presentation.

The subject matter pertaining to the claimed invention that is described within the Andrews *et al.* presentation was invented by the named co-inventors, *i.e.*, Pablo Caviedes, Raul Caviedes, Thomas B. Freeman, Juan A. Asenjo, Barbara A. Andrews, Dario Sepulveda, Christian Arriagada, and Julio Salazar Rivera. Therefore, the Andrews *et al.* presentation represents the inventors' own disclosure published less than one year prior to the effective filing date of the subject application.

"[O]ne's own invention, whatever the form of disclosure to the public, may not be prior art against oneself, absent a statutory bar." *In re Facius,* 161 USPQ 294, 301 (CCPA 1969); and MPEP §715.01(c). Therefore, under the authority of *In re Facius*, the disclosure contained in the Andrews

et al. presentation cannot be used as a reference against the applicants' claimed invention. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §102(a) is respectfully requested.

Claims 20, 22-24, 26, and 30-31 have been rejected under 35 U.S.C. §103(a) as being obvious over Takazawa *et al.* The applicants respectfully traverse.

The applicants have amended claim 18 to recite that the cells of the culture are process-forming neuronal cells of the CNS. New claim 39 also recites that the cells are process-forming neuronal cells of the CNS. The Takazawa *et al.* patent does not teach or suggest a cell culture comprising neuronal cells of the CNS. The Takazawa *et al.* patent proposes that various adherent animal cells can be cultured using the method disclosed therein. Among the over 500 cell lines listed in the table spanning columns 5-12, which the Takazawa *et al.* patent proposes can be cultured using the disclosed method, two mouse neuroblastoma cell lines, NB41A3 (ATCC No. CCL 147) and Neuro-2a (ATCC No. CCL 131), are listed (column 11, lines 12-13). The applicants note that the mouse neuroblastoma cell lines, NB41A3 and Neuro-2a, are cells of the peripheral nervous system (PNS).

Moreover, the only cells described as actually being cultured with the disclosed method are kidney cells, *i.e.*, 293 cells (human fetal kidney) and BHK 229 cells (hamster kidney). A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). As pointed out by the Examiner at page 5 of the Office Action, in a more recent publication, Grinstaff *et al.* report that human fibroblasts and umbilical vein endothelial cells lose their morphology and adhere to untreated polystyrene plates. In view of this "negative teaching", absent supporting empirical data, as provided in the subject application, one of ordinary skill in the art would not have a reasonable expectation of success in creating a cell culture comprising neuronal cells of the CNS that cluster into aggregates, as recited in claim 18 as currently amended. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Whether a proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d

1011 (Bd. Pat. App. & Inter. 1986). Only the subject application teaches a cell culture of neuronal cells of the CNS as recited in claim 18. The Takazawa *et al.* patent only provides a reasonable expectation of success in culturing kidney cells as described, not neuronal cells, and certainly not neuronal cells of the central nervous system that cluster into aggregates, as currently recited in the claims.

To reach a proper determination under 35 U.S.C. §103, the Examiner must consider whether the invention as a whole would have been obvious to one of ordinary skill in the art at the time the application was filed. Interpreting the claimed invention as a whole requires consideration of all claim limitations. In determining the differences between the prior art and the claims, the question under 35 U.S.C. §103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983).

> In determining whether the invention as a whole would have been obvious under 35 U.S.C. §103, we must first delineate the invention as a whole. In delineating the invention as a whole, we look not only to the subject matter which is literally recited in the claim in question... but also to those properties of the subject matter which are inherent in the subject matter *and* are disclosed in the specification. . . Just as we look to a chemical and its properties when we examine the obviousness of a composition of matter claim, it is this invention *as a whole*, and not some part of it, which must be obvious under 35 U.S.C. §103. *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6,8 (CCPA 1977) (emphasis in original).

The neuronal cell cultures of the subject invention are particularly advantageous for the arrest of process (neurite) extension to prevent cell death by axotomy, which usually occurs when the cells are detached from the conventional culture dishes to form a suspension for transplantation. Neurite extension is a general consequence of differentiation, which is desirable in neuronal cell transplantation therapy in order to implant a fully functional cell and to minimize the risk of the cell reverting backward in the cell cycle *in vivo* (which can be uncontrollable and lead to tumor growth, for example). Advantageously, using the cell culture of the subject invention, neurite extension is arrested, the neuronal cells form aggregates that facilitate their manipulation *in vitro* and recapitulate the cell-cell interactions that normally occur *in vivo*. Furthermore, differentiation conditions can be

applied on an as-needed basis to further differentiate the cells without neurite growth, thereby yielding a functional cell that will have enhanced survival upon transplantation. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §103 is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Amendment Transmittal Letter
Declaration by Dr. Pablo Caviedes